

**DECLARATION OF GILBERT R. GONZALES**

**[0001]** I, Gilbert R. Gonzales, hereby state and declare the following:

**[0002]** I am a named inventor on the present application, U.S. Serial No. 10/676,408 ("the '408 Application"). I have B.Sc. (1973) and M.D. (1977) degrees from the University of Arizona. I have performed research in the area of cancer pain and palliative care, including hospice patients who need alternative drug delivery, such as following gut resections in treating their cancer.

**[0003]** In addition to my research, I belong to the following scientific and medical societies: American Academy of Neurology (Facilitator, Physical Treatments of Chronic Pain, American Academy of Neurology Therapeutics and Technology and Assessment Subcommittee, May, 1992-1996; Member, American Academy of Neurology Continuum Committee on Pain, Kenneth Casey, Facilitator, March, 1994); American Pain Society; Eastern Pain Society; International Association for the Study of Pain; and the Western Pain Society.

**[0004]** I have also served on the following Editorial Boards: American Pain Society Journal, 1993 (ad hoc reviewer); Journal of Pain and Symptom Management, 1993-present (ad hoc reviewer); The Pain Medicine Journal Club Journal, 1994 - expert analyst; Pain Forum, 1999 (ad hoc reviewer); and The Clinical Journal of Pain, 2000 (ad hoc reviewer).

**[0005]** Additionally, I have held the following positions and appointments: Assistant Professor of Neurology, 1990-1992, Department of Neurology, University of Cincinnati School of Medicine, Cincinnati, Ohio; Assistant Professor of Neurology, 1992-1998 and Associate Professor of Neurology, 1998, Mayo Medical School; Vice Chairman, Department of Neurology, 1994-1998, Mayo Clinic, Scottsdale, Arizona; Assistant Adjunct Professor, 1997-1998, Department of Psychology, University of New Orleans, New Orleans, Louisiana; Associate Attending Neurologist, 1998-2002, Memorial Hospital for Cancer and Allied Diseases, New York, New York; and Associate Member, 1998-2002, Memorial Sloan-Kettering Cancer Center, New York, New York.

**[0006]** I have reviewed the references cited against the claims of the '408 Application, including U.S. Patent Nos. 6,071,539 (Robinson) and 3,012,893 (Kremzner). Robinson generally teaches effervescent granules having a controllable rate of effervescence, which are made by a hot-melt extrusion process, and include an acidic agent, an alkaline agent, a hot-melt extrudable binder capable of forming a eutectic mixture with the acidic agent and, a plasticizer. Kremzner generally teaches the preparation of gas-containing solids by gassing a fusible sugar and cooling the gasified fusible sugar below its fusion temperature to form a solid product that is fast dissolving in water to liberate gas bubbles therefrom.

**[0007]** In the present Office Action (dated August 13, 2008), the Examiner suggests that claims 27-36 and 47-50 of the '408 Application are unpatentable over Robinson in

view of Kremzner. In particular, the Examiner states that Robinson generally teaches effervescent granules having a controllable rate of effervescence, and that Robinson only fails to teach a gas dispersing component included in a solid matrix. For this limitation, the Examiner then points to Kremzner, stating that Kremzner teaches a method of enclosing a gas within a solid matrix, and so provides a gas dispersing component included in a solid matrix. The Examiner suggests that one of ordinary skill in the art would combine the teachings of Robinson and Kremzner to reach the presently claimed invention. I disagree because, prior to the '408 Application, one of ordinary skill in the art would not use such a gas-dispersing component with a medicament and would not use a gas-dispersing component or effervescent component in an oligohydrous condition.

**[0008]** The '408 Application describes and claims a formulation that includes (1) a gas dispersing component, (2) a gas-generating effervescent component, and (3) a medicament. The formulation is placed in an aqueous vehicle, such as an aqueous food or beverage, containing a minimal amount of water, such as at least 0.1 ml of water. Upon contact with even a minimal amount of water, the dispersing component releases at least one first gas, and the gas-generating effervescent component reacts to produce at least one second gas, both of which are released into the vehicle. As the formulation breaks down in the vehicle, the medicament is also released, and the released first gas disperses the effervescence of the second gas to enhance distribution

and dispersion of the medicament within the vehicle. The effervescent second gas enhances penetration of the medicament in the vehicle. The vehicle is then administered to the patient. This method of administering the medicament is particularly useful in pediatric and ostomy patients, for example, cancer patients with gastrostomies, ileostomies, jejunostomies, and colostomies. The method provides for local delivery and dispersion of medicament, which is of great need in these patients, and has not previously been effectively provided.

[0009] Prior to the '408 Application, many pharmaceutical formulations containing effervescent components have been proposed to enhance ingestion and/or absorption of active pharmaceutical ingredients. Many of these are listed in the Background section of the '408 Application. And, Robinson itself describes a composition which only includes effervescent granules. However, all of these prior formulations only include effervescent components. Unlike the invention of the '408 Application, none of them also include a gas-dispersing component to assist in the dispersal of the effervescent component and the medicament.

[0010] And this distinction is present in both pending independent claims. Independent claims 27 and 47 each recite a "pharmaceutical composition" comprising a "medicament," along with the gas-dispersing component and the gas-generating effervescent component. Thus, the gas-dispersing component and gas-generating effervescent component are used to disperse and distribute a medication in a vehicle to

be administered to a patient in need. Thus, the claimed invention of the '408 Application provides, for the first time, effervescence combined with "explosion" (provided by the gas dispersing component) to disperse a medicament, and which can operate in a substance having a minimal amount of water.

**[0011]** The Examiner argues that this invention is obvious because Robinson teaches effervescent granules, and Kremzner teaches preparing a gas-containing solid matrix. The Examiner suggests that it would have been obvious to combine Kremzner into Robinson because (1) like Kremzner, the formulation of Robinson is also water or saliva activated, and (2) combination of Robinson's effervescent granules with Kremzner's gas-fused fusible sugar composition could provide effective taste-masking.

**[0012]** However, simply because two compositions can both be placed in an aqueous vehicle (water or saliva) does not mean the two compositions should or would be combined. Gas-fused fusible sugar compositions, such as in Kremzner, (a confection commonly referred to as "pop rocks" or "popping rocks"), have never been used with a medication. Indeed, there is good reason why such compositions have never been used in such a manner. Primarily, prior to the '408 Application, one of ordinary skill in the art would not use popping rocks as a gas-dispersing component to distribute medication because the process of fusion under compression that is described in Kremzner results in a formulation in which the medicament could lack stability. And, when providing a formulation for the delivery of a medicament, the FDA

will require formulation specifications to show stability and that denaturation is not taking place. As such, one skilled in the art has never combined compositions such as those of Robinson and Kremzner. It is only the work described in the '408 Application, which goes against the conventional wisdom of those of ordinary skill in the art, that now, for the first time, provides such a combination.

**[0013]** Further, nowhere does Kremzner suggest that his composition can be used to disperse medications (nor would it, since one skilled in the art would not have used such a composition with a medicament). The only uses for the composition described in Kremzner are as a vehicle for gas storage, a carbonating agent in beverages, a leavening agent in baking, and as a carbonated hard candy (see column 3, lines 55-68). None of these uses are even remotely similar to a use to disperse a medication or medications. And nowhere does Kremzner mention any medicament as a potential ingredient of the formulation. Apart from the sugars and gas used to form the fusible sugar/gas composition, Kremzner only mentions edible acids, buffer salts, flavors, and coloring as other materials that may be added (see column 2, lines 63-70). Since one of ordinary skill in the art would not use the composition of Kremzner with a medicament, it is my view that one would not combine the composition of Kremzner with that of Robinson.

**[0014]** Further, independent claims 27 and 47 recite that the gas is adapted to be released when the composition is combined with as little as 0.1 ml of water. In my view,


one of ordinary skill in the art also would not think that subjecting the composition of Kremzner to an oligohydrous condition (i.e. a minimal water environment like apple sauce) would lead to explosion and effervescence ("explosion" referring to the release of compressed gas in popping rocks). To that end, Kremzner states that its composition can dissolve in water, but never lists any amounts of water. However, Kremzner does describe that the compositions may be used for carbonating beverages, and as hard candies. A beverage would include more than 0.1 ml of water, and a hard candy would dissolve in the mouth as a result of contact with the saliva (as described by Kremzner) – which would be present in more than 0.1 ml. Thus, Kremzner does not describe a composition that will "explode" in an oligohydrous condition including as little as 0.1 ml water. Nor does Robinson suggest an oligohydrous condition when using its composition. Thus, it is my view that it would not be obvious to combine the compositions of Robinson and Kremzner for use in an oligohydrous condition.

**[0015]** I hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Applicant Gilbert Rene Gonzales et al.  
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Further Declarant sayeth naught.

January 12, 2009  
Date

 1/12/09  
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Gilbert R. Gonzales